Primary Cutaneous Angiosarcoma of the Scalp with Cranial Invasion in a Patient with Metastatic Breast Cancer

ABSTRACT

Idiopathic cutaneous angiosarcoma (CA) of the head and neck is a distinct subtype of angiosarcoma most commonly presenting as a single or multiple purple, bruise-like patches that arise *de novo* and enlarge over several months. In clinical practice, both misdiagnosis and delayed diagnosis are frequently encountered. Here, we present a case of idiopathic CA on the scalp with invasion to the cranium in a patient with breast cancer metastatic to the brain. The patient was initially misdiagnosed and mistreated with herpes zoster and breast cancer metastatic to the skin, which led to a delayed diagnosis by two months until dermatologic evaluation. The diagnosis was then firmly established as CA based on consistent clinical and histological features. Since the tumor was inoperable, radiotherapy and chemotherapy were been considered as the appropriate adjuvant modes of therapy. Despite an initial favorable response, the disease demonstrated a rapidly progressive course and the patient succumbed to the disease within six months. This report briefly reviews the clinical and histological portrait and management options for this aggressive tumor.

KEY WORDS: Angiosarcoma, head, neck, primary, radiotherapy, breast cancer

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Angiosarcoma is a rare, highly malignant mesenchymal neoplasm derived from vascular or lymphatic endothelial cells. It composes 1 to 3 percent of adult soft-tissue sarcomas.[1] Cutaneous angiosarcoma (CA) accounts for five percent of all malignant skin tumors.[2]

CA mainly arises in three distinct clinical scenarios: 1) Sporadic idiopathic (primary) CA involving the head and neck; 2) CA secondary to long-standing lymphedema (Stewart–Treves syndrome); and 3) CA secondary to irradiation.[1,3] The prognosis of CA is poor relative to that of other skin malignancies. Therefore, early diagnosis and appropriate management are vital.[1,4,5]

CASE PRESENTATION

A 50-year-old woman was referred to us by the oncology department because of an extremely painful, red, persistent eruption present on the scalp for the previous two months. Until the time of dermatologic evaluation, she had been misdiagnosed and mistreated, initially as a case of herpes zoster and then as skin metastasis from breast cancer. Her medical history was remarkable for invasive ductal carcinoma of the left breast, for which she had undergone modified radical mastectomy, axillary lymph node dissection, and 25 sessions of radiotherapy to the breast six years prior. Sacral bone metastases from breast cancer had been detected four years ago, for which she had received 10 sessions of local radiotherapy to the sacrum.

Dermatological examination revealed an erythematous, edematous, and telangiectatic plaque with a peau d'orange appearance, roughly 15×10 cm in size and soft and tender to the touch, located on the frontal area of scalp and extending to the forehead (Figure 1).

Histologic examination of a punch biopsy specimen displayed anastomosing and atypical vascular structures of a variable size dissecting the collagen bundles in the dermis and lined by markedly pleomorphic endothelial cells (Figure 2). Immunohistochemical stains revealed positive staining for CD31 (Figure 3) and CD34.

Meanwhile, at this point, rapid clinical deterioration was observed. One month after the initial dermatological examination, the tumor had developed purplish areas and telangiectasia, and the scalp and upper eyelids had become swollen by massive edema (Figure 4). A cranial magnetic resonance imaging assessment showed invasion into the cranium by the CA, along with brain metastases from the breast cancer. Since the cutaneous lesions were not amenable to

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complete surgical excision, the patient received adjuvant radiotherapy at a cumulative dose of 50 Gy and chemotherapy with paclitaxel. Despite a favorable initial clinical response with the amelioration of pain, the patient succumbed to the disease within six months after her initial diagnosis.

DISCUSSION

Idiopathic CA of the head and neck is the most common subtype of CA, representing almost 50 percent of all CAs.[1,4] This is typically an insidious tumor found in elderly men with a median age of 70 to 75 years, arising *de novo* and showing a predilection for the scalp and central face.[1–3] Patients with fair skin tones are more commonly affected than those with darker skin.[6] Contrary to secondary subtypes of CA, no etiological factor has been proven to take part in primary CA of the head and neck.[2]

Clinically, idiopathic CA of the head and neck presents with erythematous, violaceous or dark blue macules, patches, papules, nodules, or plaques.[1,7] Lesions may be single or multifocal.[1] Apart from the scalp, involvement of the cheeks, eyelids, nose, and ears has been documented.[3,6–9] Early lesions can simulate a traumatic bruise, a hematoma, a hemangioma, an infection, or an inflammatory disorder, such as rosacea, rhinophyma, or angioedema.[1] In the great majority of patients (79.3%), the lesion is painless.[10] In advanced lesions, pain, edema, ulceration, and bleeding can confound the clinical picture.[1] Progressive chronic or episodic solid facial edema and isolated eyelid edema have been encountered in some patients.[1,6] In our patient, severe excruciating pain was the predominant symptom. Eyelid edema, worsening with rapid tumor progression, was also a prominent feature.

The diagnosis of CA is usually delayed, owing to diverse and atypical clinical presentations and the involvement of shielded areas of scalp under the hair cover.[1,4,5] In our patient, the ultimate diagnosis was delayed by two months because of preliminary misdiagnoses of herpes zoster and skin metastases from breast cancer.

Histologically, a CA is typically characterized by numerous, irregular, and anastomosing interlacing vascular channels that dissect the collagen bundles.[2,6] These are lined by atypical, pleomorphic, hyperchromatic endothelial cells with pleomorphic nuclei exhibiting a diffuse

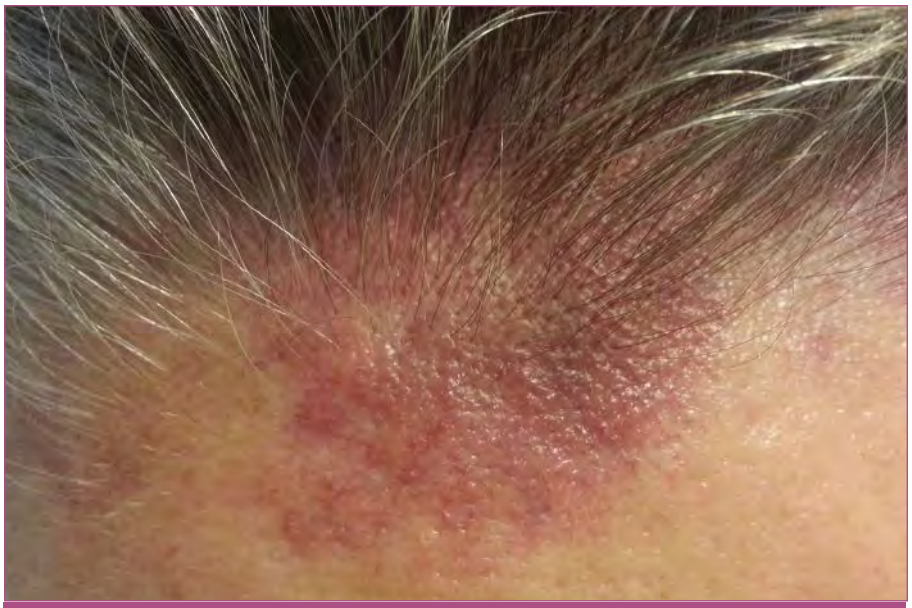

FIGURE 1. Erythematous plaque on the frontal area of the scalp with extension to the forehead

epithelioid or spindle-cell proliferation with variable mitotic activity.[3] The tumor can display a spectrum from well to poorly differentiated forms.[10–12] Immunohistochemical staining for the endothelial markers von Willebrand factor, CD31, CD34, Ulex europaeus agglutinin 1, vascular endothelial growth factor receptor, Factor VIII–related antigen and podoplanin (D2-40) can confirm the clinical and histological diagnosis.[3,11,12] Among these, the most sensitive and specific marker for endothelial differentiation is CD31.[8,9,11]

CA is clinically aggressive, with a profound risk of rapid progression, strong propensity for local recurrence, and a high capacity for metastasis to regional lymph nodes and distant organs.[1,10,11] Depending on the modality of treatment, local recurrences have been observed in 35 to 86 percent of cases.[3,5] The most common site of metastasis is the lungs, followed by the lymph nodes, bone, and liver.[8,11,12] Distant metastasis at the time of diagnosis is found in almost one-third to one-half of patients.[5,9] The reported five-year survival rate ranges from 10 to 30 percent.[1] The major clinical prognostic factor is the lesion size, with tumors less than 5cm in diameter having a better prognosis and tumors greater than 10cm in diameter foretelling an almost 100-percent mortality rate.[3,12]

The treatment of CA is challenging. For patients with clinically localized disease, wide local excision with appropriate reconstruction, aiming at achieving histologically negative margins,

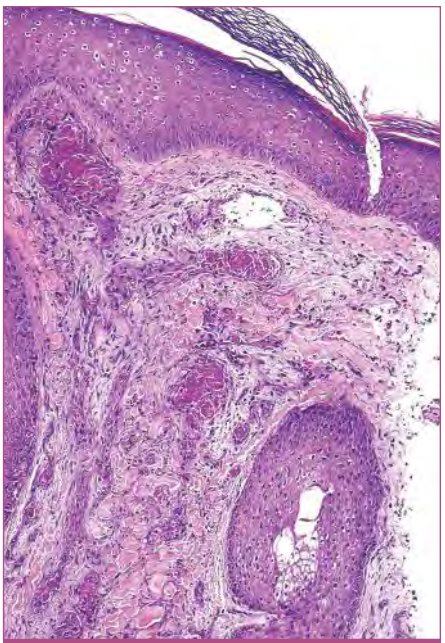

FIGURE 2. Anastomosing vascular channels lined by highly atypical endothelial cells (hematoxylin and eosin 200×)

has long been the mainstay of treatment.[1,10,14] However, complete excision with wide margins is often technically difficult due to the occurrence of CA in areas where extensive surgery will result in substantial functional impairment or in wounds that are extremely problematic to reconstruct.[13,14] Even if technically feasible, complete excision with histologically negative margins is difficult to achieve because of poor delineation of multifocal

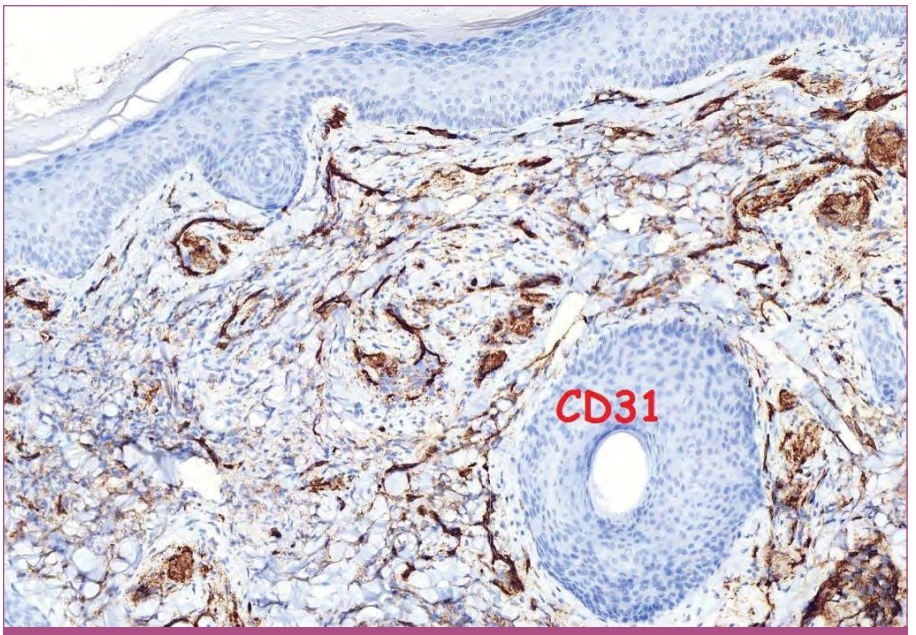

FIGURE 3. Positive staining of the tumor with CD31 (diaminobenzidine 200×)

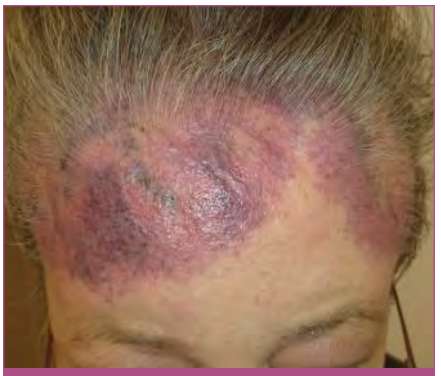

FIGURE 4. Rapidly progressing tumor with purplish areas and telangiectasia developing on the surface; note the bilateral upper eyelid edema

CAs with microscopic extensive spread beyond clinically apparent margins.[1,5,10,14]

Therefore, most studies advocate for surgical excision followed by palliative postoperative wide-field radiotherapy (>50 Gy) as the optimal approach for localized CA.[1,3–5,10,14,15] The extent of disease in our patient precluded wide surgical excision. Thus, radiotherapy and chemotherapy have remained as palliative modes of treatment.

Chemotherapy is reserved as an adjuvant therapy in patients with metastatic or locally advanced disease.[1,2,14,15] CAs appear to be particularly responsive to taxanes, owing to their antiangiogenic properties.[3,5,14] There are anecdotal reports of complete or partial remissions of radiation resistant, inoperable, or metastatic CA following treatment with liposomal doxorubicin, paclitaxel, docetaxel, gemcitabine, ifosfamide or with a combination of these agents.[1,3,4,6,12,15] Promising results have also been described with 13-cis-retinoic acid, interferon alfa-2a and recombinant interleukin-2 immunotherapy.[5]

Targeted therapy with inhibitors of vascular endothelial growth factor and its receptor or with tyrosine kinase inhibitors has shown some efficacy in CA, bringing optimism for the future. Recently, the response of programmed death-ligand 1-expressing angiosarcoma to anti-programmed cell death protein 1 therapy (pembrolizumab) has been documented.[16] Interestingly, β-adrenergic receptors constitute another potential therapeutic target in CA. Monotherapy with propranolol has been reported to reduce the proliferative index of CA and combinations of propranolol with paclitaxel, cyclophosphamide, vinblastine, methotrexate or radiotherapy have been successful in some case reports.[13,16]

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